POST-EDITED MACHINE TRANSLATION
from

RISING SUN COMMUNICATIONS LTD.

(Incorporating Rotha Fullford Leopold of Canberra, Australia)

The Nightingale Centre, 8 Balham Hill, London SW12 9EA

JAPANESE PATENT SPECIFICATION

No. J07-33768

A PYRIDINEVINYLPYRAZOLOPYRIDINE DERIVATIVE AND A PROCESS FOR THE PRODUCTION THEREOF

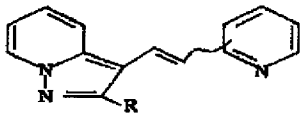
(57) (Abstract) .

(Subject) .

To put forward novel pyridine vinyl pyrazolopyridine derivatives having powerful neutrophil migration inhibitory action, a process for the production thereof, a therapeutic agent containing these.

(Construction) .

A pyridine vinyl pyrazolopyridine derivative and pharmacologically acceptable salt thereof characterised in represented by general formula (1) and a process for production thereof



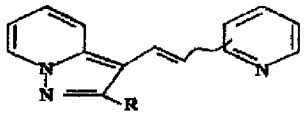
(1)

[In the formula, R denotes a lower alkyl group of carbon number 1-3].

Patent Claims.

(Claim 1)

A pyridine vinyl pyrazolopyridine derivative and pharmacologically acceptable salt thereof represented by general formula (1)

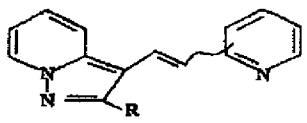


(1)

[In the formula, R denotes a lower alkyl group of carbon number 1-3].

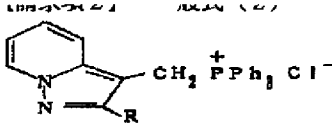
(Claim 2)

A process for the production of the compound represented by general formula (1)



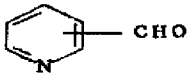
(1)

[In the formula, R has the same aforesaid meaning], characterised in reacting a compound represented by general formula (2) and the compound represented by general formula (3) in the presence of base.



(2)

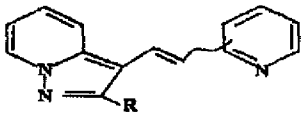
[In the formula, R denotes a lower alkyl group of carbon number 1-3].



(3)

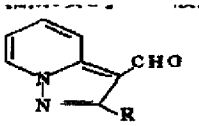
(Claim 3)

A process for the production of the compound represented by general formula (1)



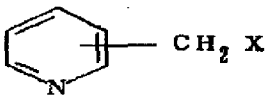
(1)

[In the formula, R has the same aforesaid meaning], characterised in reacting a compound represented by general formula (4) and the compound represented by general formula (5) in the presence of base.



(4)

[In the formula, R denotes a lower alkyl group of carbon number 1-3]

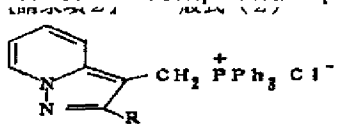


(5)

[In the formula, X denotes P+Ph3Cl- or -P(O) (OR')2 (R' denotes a lower alkyl group)].

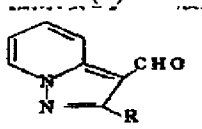
(Claim 4)

A process for the production of the compound represented by general formula (2)



(2)

[In the formula, R has the same aforesaid meaning], characterised in reducing a compound represented by general formula (4)

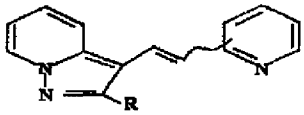


(4)

[In the formula, R denotes a lower alkyl group of carbon number 1-3], thereby forming an alcohol body, thereafter, reacting with triphenylphosphine and carbon tetrachloride.

(Claim 5)

A therapeutic agent of disease involving inflammatory cell having as an active ingredient at least one member or more of pyridine vinyl pyrazolopyridine derivatives represented by general formula (1) or acid salts thereof.



(1)

[In the formula, R denotes a lower alkyl group of carbon number 1-3].

(Detailed Description of the Invention).

(0001)

(Sphere of Application in Industry).

The compound of this invention relates to novel pyridine vinyl pyrazolopyridine derivatives having powerful neutrophil migration inhibitory action, which is useful in therapies of diseases involving inflammatory cells, such as glomerulonephritis, ulcerative colitis, Crohn's disease, Behchet's disease, chronic granulomatosis, asthma, adult respiration facilitated syndrome, emphysema, idiopathic pulmonary fibrosis, lung infection, acquired hemolytic anaemia, agranulocytosis, Goodpasture's syndrome, serum sickness, hypersensitivity pneumonitis, allergic rhinitis, atopic dermatitis, myocardial infarction, gastric ulcer, duodenal

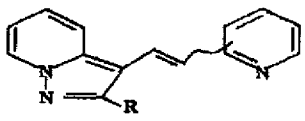
ulcer, various thrombosis, peripheral circulation insufficiency and the like, also, it relates to a process for the production thereof and a therapeutic agent containing them.

(0002)
(Technology of the Prior Art)
As pyrazolopyridine derivatives having action with respect to inflammatory cell, a compound in accordance with Kokai 59-167516 by these applicants is known and the structure thereof is acyl derivative at position 3 substituent of pyrazolopyridine backbone.

(0003)
Moreover, as silver halide photographic emulsion for a direct positive, pyrazolopyridine derivatives are known in Kokai 55-7703, Kokai 3-274546, Kokai 4-19649 and Kokai 4-158355, but they differ from the compound of this invention for the action, and they are characterised in that
the position 3 substituent of pyrazolopyridine backbone is bicyclic compound of for example benzothiazole, 1,8-naphthyridine and the like, or they are quaternary salt derivatives, and they are structurally different.

(0004)
(Problems to be Overcome by this Invention)
A number of diseases involving inflammatory cells participates are known, and effective drug having better neutrophil migration inhibitory action is strongly desired.

(0005)
(Means to Overcome these Problems)
These inventors carried out assiduous investigations on the drug which acted on inflammatory cells, as a result, discovered that pyridine vinyl pyrazolopyridine derivatives represented by the following general formula (1) had a powerful neutrophil migration inhibitory action.



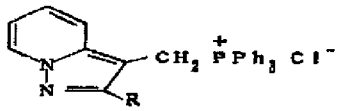
(1)

[In the formula, R denotes a lower alkyl group of carbon number 1-3].

(0006)
In general formula (1) of this invention, as "lower alkyl group of carbon number 1-3", methyl, ethyl, propyl and isopropyl group are nominated.

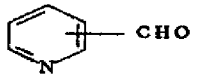
(0007)
In accordance with this invention, the compound of general formula (1) can be produced by pathway described below.

(0008)
1) The compound of general formula (1) can be produced by reacting the compound represented by general formula (2) and the compound which is general formula (3).



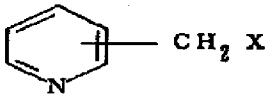
(2)

[In the formula, R denotes lower alkyl group of carbon number 1-3].



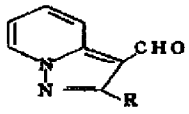
(3)

(0009)
Moreover, in the same way, the compound of general formula (1) can be produced by reacting the compound represented by general formula (5) and the compound which is general formula (4).



(5)

[In the formula, X denotes P+Ph3Cl- or -P(O) (OR')2 (R' denotes a lower alkyl group)].



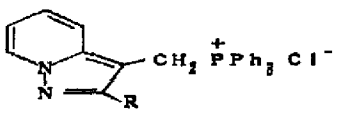
(4)

[In the formula, R denotes lower alkyl group of carbon number 1-3].

(0010)

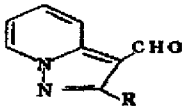
The reaction is preferably carried out in an organic solvent, for example methanol, ethanol or tetrahydrofuran and the like, in the presence of base of for example sodium alkoxide, sodium hydride or butyllithium and the like, at a reaction temperature of -60 degrees - solvent reflux temperature.

(0011)
2) The compound of general formula (2) is new, and it can be produced by reducing the compound of general formula (4) thereby forming alcohol body, thereafter, reacting with triphenylphosphine and carbon tetrachloride.



(2)

[In the formula, R has the same aforesaid meaning],



(4)

[In the formula, R has the same aforesaid meaning].

(0012)
The reductive reaction is preferably carried out with sodium borohydride for example in methanol or ethanol, and the reaction temperature is preferably room temperature - reflux temperature. Thereafter, the reaction of triphenylphosphine and carbon tetrachloride is preferably at the reflux temperature.

(0013)
It is possible that the compound of this invention (1) is made into pharmaceutically permitted non-toxic salt thereof in accordance with requirements. As example of such salts, salts of inorganic acid such as hydrochloric acid, sulphuric acid, phosphoric acid, salts of organic acid such as acetic acid, propionic acid, tartaric acid, citric acid, glycolic acid, gluconic acid, succinic acid, malic acid, glutamic acid, aspartic acid, methanesulfonic acid, and the like are nominated.

(0014)

Moreover, the compound of this invention can be used in a suitable form of drug formulation for aoral administration, oral administration or topical administration. As drug formulation, a liquid agents such as injection, syrup, emulsion, a solid agent of for example tablet, capsule agent, granules and a topical agent of for example ointment, suppository and the like are nominated.

(0015)
(Example)
Thereafter this invention is illustrated by embodiment. However, this invention is not restricted by this.

(0016)
(Reference Example 1)
(2-isopropyl pyrazolo [1,5- a] pyridine-3-yl methyl) triphenylphosphonium chloride.

(0017)
Sodium borohydride (6.35 g) was gradually added with stirring at temperature of 10-15 degrees to a mixed liquor of 3-formyl-2-isopropyl pyrazolo (1,5-a) pyridine (30.1 g) and methanol 200 ml and it was stirred for 15 minutes. It was returned to room temperature and stirred, thereafter it was poured into iced water, and it was extracted with benzene. The organic layer was dried with anhydrous sodium sulphate, and it was concentrated under vacuum. The liquid mixture of the residue (28.9 g), triphenylphosphine (79.7 g), carbon tetrachloride (60 ml) and benzene (100 ml) was heated under reflux for four hours 30 minutes. After cooling, the precipitate was recovered by filtration and was washed with benzene and then ether, and next it was dried under reduced pressure, and the target substance 71.2 g was obtained as pale yellow-coloured crystals.

(0018)
(Example 1)
(E)-2-isopropyl-3-(2-(3-pyridyl) vinyl) pyrazolo (1,5-a) pyridine hydrochloride.

(0019)
A mixture of (2-isopropyl pyrazolo [1,5-a], pyridine-3-yl methyl) triphenylphosphonium chloride (1.80 g), 3-pyridine aldehyde (0.40 ml), sodium methoxide (0.25 g) and methanol

(35 ml) was heated under reflux for 20 hours. The reaction liquor was concentrated under vacuum, and next, it was discharged into dilute hydrochloric acid, and the insolubles were eliminated by filtration, and the filtrate was made alkaline using potassium carbonate aqueous solution, and it was extracted with acetic acid ethyl ester. The organic layer was washed with saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next it was concentrated under vacuum. The residue was dissolved in ethanol-ether mixed liquor, and concentrated hydrochloric acid was added while cooling on an ice bath. The product separated as yellow powder was recovered by filtration, and it was washed with ether and next, dried, and the target substance 0.58 g (48 %) was obtained. Melting point: around 180 degrees.

(0020)

Elemental analysis value (%) as C17H17N3•HCl•H2O.

	C	H	N
Calculated value	64.25	6.34	13.22
Measured value	64.00	6.26	13.04

(0021)

(Example 2)

(E)-2-isopropyl-3-(2-(2-pyridyl) vinyl) pyrazolo [1,5-a] pyridine hydrochloride.

(0022)

The target substance which was yellow acicular crystals (28 %) was obtained in the same way as in Example 1. Melting point: around 200 degrees.

(0023)

Elemental analysis value (%) as C17H17N3•HCl•H2O.

	C	H	N
Calculated value	64.25	6.34	13.22
Measured value	64.29	6.32	13.29

(0024)
(Example 3)
(E)-2-isopropyl-3-(2-(4-pyridyl) vinyl) pyrazolo [1,5-a] pyridine hydrochloride.

(0025)
The target substance which was orange crystals (29 %) was obtained in the same way as in Example 1. Melting point: around 230 degrees.

(0026)
Elemental analysis value (%) as C17H17N3•HCl•H2O.

	C	H	N
Calculated value	64.25	6.34	13.22
Measured value	64.29	6.12	13.23

(0027)
(Test Example 1) .
Inhibition test with respect to migration ability of rabbit peripheral blood neutrophil.

Rabbit was fixed without anaesthesia at dorsal position, and blood was collected using citric acid from femoral artery. Dextran was added to the blood, erythrocyte was precipitated, thereafter distilled water was added to the supernatant liquid, and the remaining erythrocytes were haemolysed by hypotonic process. Obtained leukocyte was layered on NycoPrep (Registered Trade Name), and lymphocytes and neutrophils were separated, and neutrophils were suspended in RPMI1640 culture medium. The migration ability of neutrophils was measured using blind well chemotaxis chamber. As chemotaxis membrane, membrane of pore size 2 μm was used. The fMLP and LTB4 were used for neutrophil stimuli. The obtained results are shown in Table 1.

Rabbit neutrophil migration inhibition rate (%)

Compound	Concentration	Migration inhibition rate (%)	
	(g/ml)	fMLP	LTB4
Example 1	10^{-6}	52.7	43.8
Example 3	10^{-6}	47.8	34.1